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Expanding Precompetitive Multisector Collaborations to Advance Drug Development and Pharmacogenomics

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Drug development requires a myriad of preclinical and clinical studies to understand the pharmacokinetics, efficacy, and toxicity of new drugs in patients. To inform these studies, a common base of knowledge is required. In this commentary, we provide an overview of several multidisciplinary consortia that support precompetitive drug development and pharmacogenomics research. The goal of this commentary is to stimulate awareness of consortia that advance knowledge in clinical pharmacology.

This commentary provides many examples of consortia from multiple sectors that work together to conduct research in drug development and pharmacogenomics. Examples are selected to demonstrate differences in funding mechanisms, membership, and collaborative goals and needs. Many consortia are funded by research grants from the government (e.g., the National Institute of Health (NIH)), public-private partnerships (e.g., the European Innovative Medicines Initiative (IMI) (<https://www.imi.europa.eu/>), Horizon 2020 (<https://ec.europa.eu/programmes/horizon2020/en>)), or commercial entities (e.g., pharmaceutical and biotechnology industry). However, there

are examples of consortia, which are formed voluntarily by scientists from multiple sectors, that have no source of funding. **Table 1** and the associated **Supplementary Information** provide an extensive list of consortia in drug development and pharmacogenomics. For each consortium, the membership, funding source, and link to the relevant website are provided.

CONSORTIA FOCUSING ON DRUG DEVELOPMENT

Table 1 and the associated **Supplementary Information** provide a list of active consortia focused on drug development, including drug discovery. Four consortia

focused on scientific issues that are relevant to drug development, and in particular, drug-drug interactions are described in more detail below.

The International Transporter Consortium (ITC) was founded without financial support in 2007 by key scientists with expertise in drug metabolism, transport, and pharmacokinetics from multiple sectors (academia, industry, and the US Food and Drug Administration (FDA)). ITC investigators from the United States, Europe, and Asia are interested in the role of drug transporters in drug safety and efficacy (<https://www.itc-transporter.org/>). The first workshop held in 2008 was a collaborative effort with the FDA that resulted in a white paper on membrane transporters in drug development¹ that exemplified the aims of the FDA's Critical Path Initiative (<https://www.fda.gov/science-research/science-and-research-special-topics/critical-path-initiative>). Since 2008, a total of three workshops and two joint workshops on drug transporters in absorption, distribution, metabolism, and elimination have provided critical updates and recommendations that were incorporated into several white papers, each addressing important areas in drug development, including drug-drug interactions (DDIs), transporter polymorphisms, emerging transporters of clinical importance, *in vitro* methods for transporter evaluation, recommendations related to clinical study design, and potential clinical probes and endogenous biomarkers, among others.^{2,3} Although great advances have been made in our understanding of factors affecting transporter function and clinical relevance, challenges remain, and the knowledge gaps must continue to be addressed via collaborative efforts, such as the ITC. The

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Table 1 A list of consortia or networks consisting of members from academia, industry, and government working together to meet goals related to drug discovery and development or pharmacogenomics

Consortium name (acronym)	Goal	Members	Financial support
Drug discovery and development			
Academic Drug Discovery Consortium (AD2C)	To build a collaborative network among the growing number of university-led drug discovery centers and programs.	Academia, Industry	Industry
Accelerating Therapeutics for Opportunities in Medicine (ATOM)	The mission is to transform drug discovery by accelerating methods and tools used in drug discovery and development.	Academia, Industry	Public–private partnership
Biomarker Consortium	To discover and validate endogenous substrates for transporters involved in drug absorption and elimination.	Academia, Industry	Industry
Drug-Induced Liver Injury Network (DILIN)	To collect and analyze cases of severe liver injury caused by prescription drugs, over-the-counter drugs, and alternative medicines, such as herbal products and supplements.	Academia	NIH
Kinetics for Drug Discovery (K4DD) Consortium	To enable the adoption of drug-target binding kinetics analysis in the drug discovery decision-making process, and thereby contribute to the development of a new generation of improved medicinal products.	Academia, Industry	Industry-driven public-private partnership
Illuminating the Druggable Genome (IDG)	IDG Consortium is a U54 program funded by the NIH Common Fund with the goal of shedding light on understudied targets.	Academia	NIH
Innovation and Quality (IQ) International Consortium	Organization of pharmaceutical and biotechnology companies with the mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators, and the broader R&D community.	Industry	Industry
International Transporter Consortium (ITC)	To advance our understanding of transporter biology in drug development with the goal of improving human health.	Academia, Industry, Government	None
PET-IVIVE Consortium (2015-2019)	Predicting the role of hepatic transporters in pharmacokinetic (PK) and tissue concentrations via <i>in vitro</i> assays and drug PK and tissue concentrations in humans quantified by Positron Emission Tomography (PET).	Academia, Industry	Industry
Structural Genomics Consortium (SGC)	The SGC catalyses research in new areas of human biology and drug discovery by focusing explicitly on less well-studied areas of the human genome.	Academia, Industry	Public–private partnership
University of Washington Research Affiliate Program on Transporters (UWRAPT)	Quantifying absolute expression of transporters and enzyme in various tissues and cells to predict interindividual variability in drug clearance and tissue concentrations.	Academia, Industry	Industry
Pharmacogenomics			
Clinical Pharmacogenetics Implementation Consortium (CPIC)	Facilitating the use of pharmacogenetic tests for patient care.	Academia, Industry	NIH
French National Network of Pharmacogenetics (RNPgX)	Issue recommendations based on level of evidence whether pharmacogenetic tests are needed for patient care.	Academia, Hospital, Private laboratory	None
Industry Pharmacogenomics Working Group (I-PWG)	To improve patient care through integration of pharmacogenomics in drug development.	Industry	Industry
PharmacoGenetics and Pharmacogenomics Research (A network in the European Federation For Pharmaceutical Sciences, EUFEPS)	The Network provides a platform for experts for gathering and disseminating knowledge, determining PGx-strategies; for collaboration between academic institutions and industry; for mechanisms of setup and exchange of databases; and for gathering and promotion of knowledge about pharmacogenetics and genomics in Europe.	Academic, Industry	Academic, Industry
Pharmacogene Variation Consortium (PharmVar)	A central repository for pharmacogene variation that focuses on haplotype structure and allelic variation.	Academia, Industry	NIH
Pharmacogenomics Knowledgebase Resource (PharmGKB)	Collects, curates, and disseminates knowledge about the impact of human genetic variation on drug responses through the various activities.	No membership	NIH
Pharmacogenomics Research Network (PGRN)	To catalyze and lead research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and adverse drug effects.	Academia, Industry, Government	NIH

(Continued)

Table 1 (Continued)

Consortium name (acronym)	Goal	Members	Financial support
Pharmacogenomics Working Group (within the Global Genomic Medicine Collaborative (G2MC))	The Pharmacogenomics (PGx) Working Group works on genomic research and database projects to address severe drug-induced adverse events.	Academic, Industry	Previously was supported by NIH and US NAM, currently independent not-for-profit charitable organization
Southeast Asian Pharmacogenomics Research Network (SEAPharm)	To enable and strengthen pharmacogenomics research among the various pharmacogenomics communities within Southeast Asia, with the ultimate goal to support pharmacogenomics implementation in the region.	Academia	Public, Industry
Ubiquitous Pharmacogenomics (U-PGX)	To make effective treatment optimization accessible to every European citizen.	Clinicians, Academia researchers	European Commission
UK Pharmacogenetics and Stratified Medicine Network (UKPSM)	To develop collaborative partnerships and to synergize research into stratified/personalized/precision medicine across the UK, and internationally, to support its adoption into the clinic.	Academia, Industry, Government	European Commission, UK Government, Meetings
Pharmacogenomics (focusing on a specific disease, drug class, or adverse drug event)			
African American Cardiovascular Pharmacogenomics Consortium (ACCOUNT)	To ensure that all people, including African Americans, benefit fully from precision medicine.	Clinicians, academia researchers, community leaders, and patients	NIH
Canadian Pharmacogenomics Network for Drug Safety (CPNDS)	To solve drug safety problems by developing genetic tests that predict which patients are at risk of serious adverse drug reactions.	Academia, Industry	Industry
Epilepsy Pharmacogenomics Consortium (EPIPGX)	EPIPGX is a unique pharmacogenomics project which brings together renowned scientists from various academic institutions and SMEs throughout Europe.	Academia, small to mid-size enterprise	None
Genetics of Osteosarcoma (GO-consortium)	Understanding and optimizing osteosarcoma treatment through genetics.	Academia	Public
Metformin Genetics (MetGen Plus)	Diabetes studies that have genetic data and metformin and other antidiabetes drug treatment outcome measures.	Academia	None
Pharmacogenomics in Childhood Asthma (PICA)	Bring together asthma studies that have genetic data and treatment outcome measures.	Academia	None
Prediction ADR Consortium (Prediction-ADR)	Discover the genetic factors predisposing patients to adverse drug reactions (ADRs) from cardiovascular disease (CVD) drugs.	Academia	European Community
The International Serious Adverse Events Consortium (ISAEC)	To identify DNA-variants useful in understanding the risk of drug-related serious adverse events (SAEs).	Academia, Industry, Government	Non profit
The Pharmacogenomics of Clozapine-Induced Myocarditis (PROCLAIM) Consortium	To uncover genomic markers that could be used preemptively by clinicians to identify those patients at highest risk for myocarditis from clozapine therapy and identify the mechanism by which clozapine induces myocardial inflammation and damage.	Academia	Public

The hyperlink and references published by the consortia are listed in **Supplementary Information**. IVIVE, *in vitro* to *in vivo* extrapolation; NIH, National Institutes of Health; SMEs, small and medium-sized enterprises; US NAM, US National Academy of Medicine.

fourth workshop will occur on March 8–9, 2021, with input from ITC members.

University of Washington Research Affiliate Program on Transporters (UWRAPT) was established by Dr. Jashvant Unadkat at the University of Washington in 2012 through support from pharmaceutical companies (<https://sop.washington.edu/uwrapt/>). The goal of UWRAPT is to better

understand and predict interindividual variability in pharmacokinetics and pharmacodynamics of drugs. Specifically, UWRAPT aims to predict transport-mediated drug disposition including tissue drug concentrations using the relative expression factor (REF), which relies on quantification of transporter proteins in various human/animal tissues and cells using quantitative targeted proteomics

(liquid chromatography–tandem mass spectrometry). Key findings of UWRAPT research fall into two main categories: (i) quantification of transporters and enzymes in various human and animal tissues,⁴ including those obtained from diseased (e.g., cirrhosis)⁵ and pediatric populations;⁶ and (ii) the use of these data for *in vitro* to *in vivo* extrapolation of drug disposition (including tissue

concentrations) mediated by transporters to predict drug disposition and tissue concentrations, verified through imaging modalities.⁷ See **Supplementary Information** for a list of publications from UWRAPT.

The Biomarker Consortium was founded recently in Japan by Drs Hiroyuki Kusuha and Yuichi Sugiyama through support from industry. Many challenges remain in the prediction of transporter-mediated DDIs. These include induction and inhibition of transporters, as well as the effects of genetic polymorphisms in modulating DDIs. The goals of this consortium are to advance the characterization of endogenous substrates to provide compelling evidence that endogenous compounds are surrogate probes to quantitatively predict transporter-mediated DDIs and to establish physiologically-based pharmacokinetic models for predicting the effects of investigational compounds on endogenous compounds. To achieve these goals,

this project will provide evidence at three levels: (i) in vitro data, (ii) animal data, and (iii) clinical data to increase the robustness of the physiologically-based pharmacokinetic models. Finally, the project will disclose the data to support the rationale for use of the endogenous probes in a publicly accessible database and in published manuscripts. Our most recent finding using coproporphyrin I as an endogenous biomarker will serve as a model for this consortium⁸ (**Figure S1**).

The Innovation & Quality (IQ) Consortium is a dynamic and technically focused organization that impacts many areas of pharmaceutical development and regulation. Membership is only opened to pharmaceutical industry. IQ supports many leadership groups and working groups focusing on issues in pharmaceutical science including the Translational and ADME Sciences Leadership Group, which focuses on studies related to drug absorption,

distribution, metabolism, and elimination, the Clinical Pharmacology Leadership Group, and others (<https://iqconsortium.org/about/>).

Other consortia and networks relevant to drug discovery and development that are funded by NIH or public-private fundings include the Accelerating Therapeutics for Opportunities in Medicine (ATOM) consortium, Drug-Induced Liver Injury Network (DILIN), Kinetics for Drug Discovery (K4DD) consortium, Illuminating the Druggable Genome (IDG), and Structural Genomics Consortium (SGC) (see **Table 1**, **Supplementary Information**).

CONSORTIA FOCUSING ON PHARMACOGENOMICS

Pharmacogenomics research is focused on understanding how an individual's genes affect his or her response to medicines. Many of the networks or consortia that



Figure 1 Illustration of multidisciplinary consortia that support precompetitive drug development and pharmacogenomics research.

focus on pharmacogenomics research are founded in the United States or Europe but include researchers around the world (**Table 1**, **Figure 1**, and **Supplementary Information**). Furthermore, many pharmacogenomics consortia study multiple ethnic groups and disease-related populations. Below, we describe the Pharmacogenomics Research Network (PGRN) as an example of a broad-based pharmacogenomics research consortium, followed by a brief description of disease-specific or drug-specific pharmacogenomics research consortia.

The PGRN is an NIH-funded program whose mission is to catalyze and lead research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and adverse drug effects. From 2000 to 2015, a total of 16 pharmacogenomics research groups, 7 network resources, and a Pharmacogenomics Knowledge Base have been supported by various NIH Institutes, led by the National Institute of General Medical Sciences. Since 2015, the PGRN has included three specialized centers (P50 grants) and six resources (R24 grants) (<https://www.pgrn.org/research-pages.html>).⁹ In 2015, the PGRN membership structure was opened, and there are currently over 600 members globally who are active in pharmacogenomics research, teaching, and clinical work. Members avail themselves of activities and resources coordinated by the PGRN Hub, including annual scientific meetings, a website rich in pharmacogenomics research tools and news (www.pgrn.org), social media posts, monthly Research in Progress Seminars, and quarterly member-wide calls. The major scientific accomplishments of PGRN-funded researchers include discovery of genetic polymorphisms in genes that are critical for disposition of and response to many drugs, including those used to treat cancer and cardiovascular, respiratory, neuropsychiatric, and rheumatologic diseases. Additional accomplishments include application of genome-wide association methods to pharmacogenomics (<https://www.pgrn.org/riken-publications.html>), functional genomics studies of common and rare variants, development and utilization of induced pluripotent stem cells, and clinical implementation and standardization of pharmacogenomics testing (see **Data S1**, reading lists to learn more about PGRN).

Future directions

Financial support from NIH for the PGRN will end on June 30, 2020. PGRN is actively exploring various partnerships and mechanisms within the United States and globally to foster its continued leadership role in pharmacogenomics research.

In addition to the PGRN, there are at least 20 pharmacogenomics consortia where researchers from around the world share data and knowledge to answer questions in pharmacogenomics. These consortia may focus on particular drug classes, diseases, or adverse drug events (**Table 1**, **Supplementary Information**). Drug-specific pharmacogenomics consortia are formed (see <https://www.pgrn.org>) to pool and expand samples for increased power in pharmacogenomics research and to bring scientists and clinicians together to participate in study design, sample collection, and data analysis and interpretation. An example of a drug-specific consortium is MetGen Plus (formerly MetGen, see <https://www.pgrn.org/metgen.html>). This consortium originally began with a focus on identifying pharmacogenomic factors that associate with response to metformin, which is first-line therapy for type 2 diabetes. Motivated by common interest, the original goal of the consortium was to replicate phenotypic and genetic findings relating to metformin response through collaboration.¹⁰ This goal expanded to include other antidiabetic drugs. Examples of disease-focused and adverse drug reaction-focused pharmacogenomics research consortia are the African American Cardiovascular Pharmacogenomics Consortium (ACCOUNT), Genetics of Osteosarcoma (GO-Consortium), The International Serious Adverse Events Consortium (ISAEC), and the Prediction ADR Consortium (Prediction-ADR). In addition, there are many other consortia, which were established previously, but have sunsetted due to completion of the project or lack of funding (e.g., see <https://www.pgrn.org/riken-projects.html>).

CONCLUSIONS

Diverse consortia exemplified in this perspective have greatly enhanced precompetitive research in drug development sciences and pharmacogenomics. Disease-specific scientific consortia have facilitated and empowered large genome-wide association

studies of human disease. Increasingly, drug-specific pharmacogenomics consortia are enabling genomewide studies of pharmacogenomics phenotypes (**Table 1**). It is envisioned that such consortia will increase in number as only a fraction of approved drugs have been studied using genomewide approaches. Similarly, multisector consortia such as the ITC, the Biomarker Consortium, and UWRAPT have enabled precompetitive research by providing much-needed expertise and knowledge that informs drug development. Though some consortia end naturally when their purpose is fulfilled, sustaining consortia is frequently challenging, often because of funding issues. Most consortia are formed by motivated scientists, often from academia, with industry partners. A by-product of many of these consortia is that they support global collaborations and scientific exchange in drug development and pharmacogenomics. In the future, consortia focused on pharmacogenomics, biomarkers, special populations, and modeling and simulation of new drugs and therapies, as well as many older drugs, will be formed to advance precision medicine. Clinical pharmacologists should continue to support these scientific consortia through membership, funding, and active participation.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Figure S1. The newly established biomarker consortium to discovery and validate endogenous substrates for transporters involved in drug absorption and elimination. Three main approaches are illustrated in this figure.

Supplementary Reading List

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CONFLICT OF INTEREST

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